Drug Discovery and Development
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“Those who have knowledge, don’t predict. Those who predict, don’t have knowledge.”

Lao Tzu, 6th Century BC Chinese Poet
I. Background

II. The R&D Landscape

III. Innovation & Transformation

IV. The Preclinical Development Process

V. Clinical Trials in CNS Drug Development
Serendipity or Good Science: Building Opportunity

Hoffman

Osterloh
I. Background
Challenges: Drug Development in the “New Normal”

We used to talk about a “Valley of Death”.....

http://fastercures.blogspot.com/2010/09
Drug Development Process
Drug Development Process

Discovery, Screening, R & D
- FDA IND Review
  - Avg. 6.5 yrs
  - 30 days
  - FDA evaluates submission

Clinical Trials
- Phase I
- Phase II
- Phase III
  - Avg. 1.5 yrs
  - Avg. 2 yrs
  - Avg. 3.5 yrs
  - FDA NDA Review
  - Avg. 1.2 yrs
  - FDA evaluates submission

Develop Manufacturing and Marketing Plan
- FDA Monitors Company Compliance

New Drug Launch
- Post Market Activity
Biopharmaceutical Drug Development: Attrition

Drug Discovery
- 10,000 Compounds
- 5 years

Pre-Clinical
- 250 Compounds
- 1.5 years

Clinical Trials
- 5 Compounds
- 6 years
  - Phase I: 20-100 Volunteers
  - Phase II: 100-500 Volunteers
  - Phase III: 1000-5000 Volunteers

FDA Review
- NDA Submitted
- 2 years

Large Scale Manufacturing / Phase IV
- 1 FDA Approved Drug
- 2 years

II. The Research & Development Landscape
Current Industry Landscape

Discovery: $281/$824 million

Development: $592/$954 million

PhRMA Member Company R&D Expenditures: 1995–2012

*Estimated for Calendar Year (CY) 2012.

Research & Development Spending: Return on Investment

Saltzmann (2009)
III. Innovation and Transformation
<table>
<thead>
<tr>
<th>Year</th>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Category</th>
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</thead>
<tbody>
<tr>
<td>1986</td>
<td>Fluvoxamine</td>
<td>(Luvox; Solvay)</td>
<td>SSRI</td>
</tr>
<tr>
<td>1987</td>
<td>Fluoxetine</td>
<td>(Prozac; Lilly)</td>
<td>SSRI</td>
</tr>
<tr>
<td>1992</td>
<td>Sertraline</td>
<td>(Zoloft; Pfizer)</td>
<td>SSRI/NRI</td>
</tr>
<tr>
<td>1993</td>
<td>Venlafaxine</td>
<td>(Effexor; Wyeth)</td>
<td>SSRI/NRI</td>
</tr>
<tr>
<td>1996</td>
<td>Bupropriion</td>
<td>(Wellbutrin; Wyeth)</td>
<td>SNRI/DRI</td>
</tr>
<tr>
<td>2002</td>
<td>Escitalopram</td>
<td>(Lexapro; Forrest)</td>
<td>SSRI</td>
</tr>
<tr>
<td>2004</td>
<td>Duloxetine</td>
<td>(Cymbalta; Lilly)</td>
<td>SSRI/NRI</td>
</tr>
<tr>
<td>2008</td>
<td>Devenlafaxine</td>
<td>(Pristiq; Wyeth/Pfizer)</td>
<td>SNRI</td>
</tr>
<tr>
<td>2011</td>
<td>Vilazidone</td>
<td>(Vybrid; Forest Labs)</td>
<td>SSRI/5HT1a</td>
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</tbody>
</table>
Personalized Medicine

Less Impersonal Medicine: Clinical Segmentation Instead of Pharmacogenetic Segmentation

- Empiric therapy Non-responders
- Pt. subsets (e.g., aspirin-induced asthma)
- Age Sex Race
- Drug-drug interactions
- Tolerability/Safety
- Contra-indications
- Co-morbidities
IV. Discovery and Preclinical Development
Discovery and Preclinical Development

Lead Selection and Optimization (iterative) → Drug Candidate Confirmation → Preclinical Drug Characterization

Efficacy Assessment: Does it work?

ADME Profiling: How can it be delivered and what does the body do?

Toxicology/Safety Pharmacology Assessment: Is it safe?

Pharmaceutics: Is the manufacture viable and controllable?

Adapted from TetraQ
Clinical Development: Phase I Assumptions & Phase II Considerations
### Figure 13: Increasing Complexity of Clinical Trials

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<thead>
<tr>
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<tbody>
<tr>
<td>Total Procedures per Trial Protocol (median) (e.g., bloodwork, routine exams, x-rays, etc.)</td>
<td>105.9</td>
<td>166.6</td>
<td>57%</td>
</tr>
<tr>
<td>Total Investigative Site Work Burden (median units)</td>
<td>28.9</td>
<td>47.5</td>
<td>64%</td>
</tr>
<tr>
<td>Total Eligibility Criteria</td>
<td>31</td>
<td>46</td>
<td>58%</td>
</tr>
<tr>
<td>Clinical Trial Treatment Period (median days)*</td>
<td>140</td>
<td>175</td>
<td>25%</td>
</tr>
<tr>
<td>Number of Case Report Form Pages per Protocol (median)</td>
<td>55</td>
<td>171</td>
<td>227%</td>
</tr>
</tbody>
</table>

*These numbers reflect only the “treatment duration” of the protocol.

Phase II Clinical Trial Considerations

- Proof of Efficacy and Safety
- Time & Cost
- Reliability of Trial Designs
  - Placebo Response
  - Patient Populations
Questions About the Placebo Response

Is the improvement in patients given a placebo:

– result of the placebo itself?
– due to natural fluctuations in the progression of the disease?
– a regression toward the mean?
– due to non-specific, treatment effects?
– due to patients’ and clinicians’ expectations?
Figure 15: Unsuccessful Alzheimer’s Drugs in Development, 1998 – 2011
Total unsuccessful drugs=101

Thank you for your time and attention